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# Blunted temperature and cortisol responses to ipsapirone in major depression: lack of enhancement by electroconvulsive therapy

Baruch Shapira, Michael E. Newman, Yevgenia Gelfin, Bernard Lerer *

*Biological Psychiatry Unit, Hadassah-Hebrew University Medical Center, Ein Karem, Jerusalem, 91120, Israel*

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**Abstract**

Depression has been shown in some studies to be associated with a reduction in hypothalamic 5-$HT_{1A}$ receptor function, as indicated by reduced hormone and/or hypothermic responses to 5-$HT_{1A}$ agonists such as ipsapirone. The hypothermic response to ipsapirone was reduced in depressed patients treated with amitriptyline. Hormone and hypothermic responses to 5-$HT_{1A}$ agonists were reduced in normal subjects administered specific serotonin reuptake inhibitors. Effects of electroconvulsive therapy (ECT) on 5-$HT_{1A}$ receptor-mediated responses in humans have not been reported. In the present work, ten depressed patients and 15 control subjects were challenged with placebo and with 0.3 mg/kg ipsapirone, administered 48 h apart in a randomised double blind design. Hypothermic, growth hormone (GH) and cortisol responses were measured. Seven of the depressed patients were treated with a course of ECT, and placebo and ipsapirone challenges were repeated 24 and 72 h after the last treatment. The cortisol response to ipsapirone was significantly reduced in the depressed patients compared with controls. The hypothermic response to ipsapirone was totally abolished in the depressed patients. When tested after a course of ECT, the seven depressed patients again showed reduced or blunted responses. We conclude that hypothalamic 5-$HT_{1A}$ receptor function is reduced in depression. In contrast to the effects of electroconvulsive shock (ECS) on postsynaptic 5-$HT_{1A}$ receptor function in animals, which have chiefly been measured in the hippocampus using electrophysiological techniques, ECT in humans does not induce an increase in

* Corresponding author. Tel.: +972-2-6777185; fax: +972-2-6439294.
*E-mail address:* lerer@cc.huji.ac.il (B. Lerer).


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sensitivity of post-synaptic 5-$HT_{1A}$ receptors in the hypothalamus. 

*Keywords:* Depression; Electroconvulsive therapy; Serotonin; 5-$HT_{1A}$ receptor; Ipsapirone; Hypothalamus

## 1. Introduction

Although there is much evidence for a dysfunction of brain serotonergic systems in major depression, most of this is indirect (Maes and Meltzer, 1995). One of the most fruitful approaches to study neurotransmitter receptor function in depressed patients has been the use of neuroendocrine challenge tests. Results obtained with the fenfluramine challenge test (reviewed by Newman et al., 1998) have in general indicated blunting of prolactin and cortisol responses in depressed patients, although some recent studies (Park et al., 1996; Kavoussi et al., 1998) have failed to show this. The exact mechanism of fenfluramine-induced hormone release is still uncertain and may involve either release of 5-HT, in which case its mechanism is essentially pre-synaptic, or direct stimulation of post-synaptic serotonin 5-$HT_{2A/2C}$ receptors. Neuroendocrine challenge tests with other agents such as L-tryptophan (Heninger et al., 1984; Cowen and Charig, 1987) or clomipramine (Golden et al., 1992; for review see Power and Cowen, 1992) have shown essentially similar results with blunting of the prolactin and/or growth hormone (GH) responses in depression. The ACTH and cortisol responses to the 5-HT precursors tryptophan and L-5-hydroxytryptophan (L-5-HTP) were however increased in depressed patients compared with control subjects in some studies (Meltzer et al., 1984; Maes et al., 1989).

More specific information about serotonergic function can be obtained using 5-$HT_{1A}$ receptor agonists, of which several are available. The effects of 5-$HT_{1A}$ receptor agonists on temperature regulation and hormone release provide a useful avenue for evaluating the functional sensitivity of 5-$HT_{1A}$ receptors in animals and man. The effect of the 5-$HT_{1A}$ agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) to induce hypothermia has been shown in several animal studies. Although a pre-synaptic mechanism has been suggested (Goodwin et al., 1985a, 1987a; Hillegaart, 1991), the bulk of the evidence indicates that the hypothermic effect of 8-OH-DPAT is mediated via post-synaptic 5-$HT_{1A}$ receptors in the hypothalamus (Hjorth, 1985; Hutson et al., 1987; O'Connell et al., 1992; Millan et al., 1993). 5-$HT_{1A}$ receptor stimulation also evokes ACTH and corticosterone release in rodents, via an effect on corticotrophin releasing factor in the paraventricular nucleus of the hypothalamus (Koenig et al., 1987; Gilbert et al., 1988; Haleem et al., 1989; Bagdy and Makara, 1994).

Ipsapirone, a centrally acting pyrimidinylpiperazine derivative, (Traber and Glaser, 1987), has a radioligand binding profile very similar to that of 8-OH-DPAT (Peroutka, 1988). Iipsapirone (0.3 mg/kg PO) induces a hypothermic response in normal human subjects (Lesch et al., 1990a; Gelfin et al., 1995). The hypothermia is dose-related, attenuated by the non-selective 5-HT receptor antagonist, metergoline, completely antagonized by the non-selective β adrenoceptor but selective 5-$HT_{1A}$/